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10/582,674	06/12/2006	Herve Perron	128125	7417

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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	PAPER NUMBER
1649	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,674	PERRON ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4 and 6-15* is/are pending in the application.

4a) Of the above claim(s) *11-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6,7 and 10* is/are rejected.

7)☒ Claim(s) *8 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 11 March 2009 have been entered. Claims 2 - 4 and 6 - 15 are pending.

Election/Restrictions

2. Claims 11 - 15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2 July 2008.

3. This application contains claims 11 - 15 drawn to an invention nonelected with traverse in the reply filed on 2 July 2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Claims 2 - 4 and 6 - 10 are under examination in the present office action.

Withdrawn Rejections and Objections

5. The following rejections and objections set forth in the previous office action are withdrawn:

A. The rejection of claim 3 under 35 USC 102(b) is withdrawn in light of the arguments. While Roecklin teaches using an anti-GM2AP antibody to detect this protein in the urine from human MS patients, the reference does not explicitly teach the step of "demonstrating the formation of a complex consisting of the heterocomplex and the antibody" as recited in claim 3.

B. The rejection of claims 2 - 5 and 10 under 35 USC 103(a) as obvious over Roecklin in view of Hornbeck is withdrawn. While Roecklin teaches using an anti-GM2AP antibody to detect this protein in the urine from human MS patients, the reference does not explicitly teach the step of "demonstrating the formation of a complex consisting of the heterocomplex and the antibody" as recited in claim 3 or of "demonstrating the formation of a complex consisting of the heterocomplex and the two antibodies" as recited in claim 4.

Maintained Rejections

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2 and 10 stand rejected under 35 U.S.C. 102(b) as being anticipated by Roecklin (WO 01/05422, of record). Applicant is reminded that U.S. Patent 7,081,354 is a translation of the '422 publication. References to specific passages of text are to the '345 patent.

This rejection is maintained for the reasons of record and explained in further detail below. Briefly, Roecklin teaches how to purify a cytotoxic factor from urine of patients with multiple sclerosis. See for example column 46 line 55 - column 48 line 22. Note that at each step of the purification process, (ammonium sulfate precipitation, purification, reverse chromatography), the cytotoxic activity was tested. At column 48 lines 17 - 22, Roecklin teaches that "[t]he toxic activity of the proteins contained in each fraction collected after elution was determined with the aid of the MTT test. Only fraction 21 exhibiting a significant toxic activity was retained." Clearly, the reference shows how to isolate a particular fraction that has cytotoxic activity.

Roecklin also provides evidence that the isolated cytotoxic factor comprises GM2AP (also known as GM2 activator protein) and calgranulin-B, which is a synonym for MRP14. See for example column 50 line 45 - column 51 line 22. While Roecklin does not specifically identify that the lipid GM2 is present in the complex, it nonetheless must be present, since the instant specification indicates that the method of purification (ammonium sulfate precipitation, purification, and reverse-phase chromatography) is suitable for purifying the complex.

Applicant argues, at pp. 6 - 7 of the remarks filed 11 March 2009, that the procedures detailed in Examples 2 and 3 of the present specification result in isolation of the individual proteins GM2AP and MRP14, not the heterocomplex as claimed. According to applicant, since the procedures detailed at Examples 2 - 3 of the present specification are the same as those in Roecklin, the prior art reference teaches isolation of the proteins, not the complex. According to applicant, the procedures are designed to eliminate lipids and therefore cannot be used to detect the lipid GM2.

Applicant's arguments have been fully considered but they are not persuasive. With respect to the argument that the methods disclosed by Roecklin result in isolation of the proteins, not the complex, the argument is not persuasive because Roecklin in does teach how to isolate Fraction 21, and provides evidence that it is cytotoxic. With respect to the argument that the procedures cannot be used to purify lipids, the examiner is unable to find any step in the

procedures detailed from column 46 line 55 - column 48 line 22 that would result in the loss of lipids. While it is possible that the Western blotting procedures used to identify the proteins in fraction 21 (i.e. separating the samples on an SDS-Tricine gel after incubating with β-mercaptoethanol) may result in loss of lipids, or in separation of lipids from the complex, this step was used by Roecklin to confirm the identity of the protein components, and clearly is not a necessary step for the isolation as claimed. The isolation procedure ends at column 48 line 22.

Applicant also argues that "isolation and detection of the heterocomplex is described in the procedures and protocols outlined in Examples 8 - 11" of the present specification. The examiner has closely reviewed those sections of the specification and has determined that they do not support applicant's arguments. Examples 8 - 9, beginning on p. 46, are drawn to development of an ELISA, whereas independent claim 2 requires a single step, namely isolating the heterocomplex. Example 10 is drawn to specific examples of detecting the heterocomplex with the ELISA assay, and example 11 is drawn to performing the ELISA on human urine samples. While the ELISA is one way to isolate and detect the heterocomplex, the methods of claims 2 and 10 can be performed in other ways, including the methods detailed at column 46 - 48 of Roecklin.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2 - 4, 6 - 7, and 10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Roecklin (WO 01/05422, of record) in view of Hornbeck Hornbeck 2000 (Current Protocols in Molecular Biology 11.2.1 – 11.2.22) and Perron 2004 (6th International Symposium on Neuroviroloogy and the HIV Neuroprotection Workshop, September 10 – 14, 2004, published in Journal of Neurovirology 10 (Suppl. 3):p. 124).

This rejection is maintained for the reasons previously made of record and explained in further detail herein. Roecklin teaches methods to detect cytotoxic complexes in urine from normal human patients and patients with multiple sclerosis. Roecklin teaches that ELISA assays, encompassed by claims 3 - 4 and 6 - 7, can be used to detect GM2AP, which is part shown by Roecklin to be cytotoxic and present in the urine of MS patients. Roecklin teaches methods of using capture and detection antibodies, which is on point to claims 6 - 7; see for example column 55 lines 4 - 25. Note that an anti-GM2AP antibody was used as a capture antibody, and an anti-rabbit IgG antibody was used as a detection antibody. However Roecklin does not explicitly teach the steps of "demonstrating the formation of a complex consisting of the heterocomplex and the antibody" as recited in claim 3 or of "demonstrating the formation of a complex consisting of the heterocomplex and the two antibodies" as recited in claim 4.

Hornbeck teaches several types of ELISA protocols, including the antibody-sandwich assay, which uses two antibodies, one being a capture antibody and the other being a detection antibody. See for example pages 11.2.8 – 11.2.10. This is on point to claims 4 and 6 - 7. Hornbeck teaches that the antibody sandwich form of ELISA is particularly suited to detecting soluble antigens, and it is 2 – 5 times more sensitive than those in which the antigen is bound to the solid phase. However Hornbeck does not teach assays for detecting the heterocomplex of GM2AP/GM2/MRP14 as recited in claim 2.

Perron teaches that the cytotoxic factor specifically found in the urine of patients with multiple sclerosis is a heterocomplex comprised of GM2AP, S100A9 (which is synonymous with MRP14; see for example Roecklin '345 patent page 2, third cited reference (by Rafferty et al.), which identifies the two terms as synonymous), and GM2. This is on point to claim 2, drawn to a method of detecting a heterocomplex comprising GM2AP, GM2, and MRP14, claims 3 - 4, drawn to methods comprising demonstrating the formation of a complex between the heterocomplex and antibodies, as well as claim 6, which is on point to detecting two separate proteins within the complex. However Perron does not teach methods of detection using at least two antibodies as recited in claim 6.

It would have been obvious to one of ordinary skill in the art to modify the methods of Roecklin to use antibodies in ELISAs as taught by Hornbeck, and to demonstrate the formation of a complex between those antibodies and the GM2/GM2AP/MRP14 heterocomplex, as suggested by Hornbeck and by Perron. The motivation to do so would be to develop an assay with high sensitivity for the heterocomplex. It would be reasonable to expect success, as the methods of Hornbeck are general and can be applied to many ELISAs, Furthermore, Perron teaches that MRP14 forms a heterodimer with GM2AP, and that this dimer is stabilized by GM2. That is, Perron teaches that the heterocomplex recited in independent claim 2 is present is MS patients and is gliotoxic, thereby guiding one of ordinary skill to develop a sensitive assay to detect this particular heterocomplex.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

At p. 9 first paragraph of the remarks filed 11 March 2009, applicant argued that Perron does not cure the deficiencies of Roecklin and Hornbeck. The examiner respectfully disagrees and believes that the rejection set forth at pp. 5 - 6 of the office action mailed 11 September 2008, along with the explanation above, shows exactly why the reference by Perron cures any deficiencies of Roecklin and Hornbeck.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2 and 10 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 - 4 and 6 - 7 of U.S. Patent No. 7,510,843. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass methods of isolating a complex comprising calgranulin-B, also known as MRP14. Note that SEQ ID NOs:17 and 63 - 65, recited the claims of the '843 patent, are calgranulin-B and fragments thereof; see '843 patent, column 15 second paragraph and column 16 first paragraph. As the sole step recited in present claim 2 is isolating, and the '843 patent claims a method of detecting, which is indistinct from isolating since the antibody-based methods of detection will isolate the complex, the issued claims conflict with the currently pending claims.

A substantially similar rejection over pending application 11/450360 was made in the previous office action. Applicant traversed and argued that the rejection be held in abeyance as the patent had not issued. Applicant had paid the issue fee on 17 February 2009, prior to the filing of the present response. While the patent itself had not issued, it appears that such issuance was imminent at the time the present response was filed. Applicant did not traverse the examiner's determination that the claims in fact conflicted.

9. Claims 2 and 10 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 - 9 of U.S. Patent No. 7,081,345. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass isolating a cytotoxic complex comprising GM2AP. Applicant argues, at p. 9 of the remarks filed 11 March 2009, that Roecklin '345 patent does not anticipate the claimed invention. However, the methods of claims 8 - 9 of the Roceklin patent will result in isolation of the complex, as claimed.

Conclusion

10. Claims 2 - 4, 6 - 7, and 10 are rejected.

11. Claims 8 - 9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
May 27, 2009